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CASE REPORT

Severe *Plasmodium vivax* cerebral malaria complicated by hemophagocytic lymphohistiocytosis treated with artesunate and doxycycline

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Abstract
Malaria-related hemophagocytic lymphohistiocytosis is a rare, potentially fatal, hyperinflammatory disease entity which can be challenging to diagnose and treat. It is usually associated with *Plasmodium falciparum* infection. It is less frequently associated with *Plasmodium vivax*. Here we report an unusual case of a 23-year-old healthy Nigerian man who presented with fever, microangiopathic hemolytic anemia, acute renal failure, and confusion, and was diagnosed as having cerebral malaria-related hemophagocytic lymphohistiocytosis caused by *P. vivax* infection. He was successfully treated with intravenous artesunate and doxycycline with dramatic clinical improvement.

Introduction

Malaria continues to remain a major health burden worldwide. According to the World Malaria Report 2015, the estimated number of malaria cases was 214 million and the number of deaths was 438,000 in 2015 alone [1]. The World Health Organization defines cerebral malaria as a clinical syndrome caused by *Plasmodium falciparum* infection manifesting as coma (defined with Glasgow Coma Scale of less than 11 in adults and Blantyre Coma Scale of less than 3 in children) persisting for more than 30 minutes after termination of seizure and no other cause of explanation for the coma [2]. Another rare complication of malaria is

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hemophagocytic lymphohistiocytosis (HLH), which is a syndrome characterized by multisystem inflammation that results from prolonged and excessive activation of the antigen presenting cells (macrophages and histocytes) and CD8+ T cells that leads to phagocytosis of hematopoietic cells [3]. HLH compromises two different conditions: (1) the primary (familial) form that is usually seen during infancy or childhood; and (2) the secondary HLH which results from an excessive immune reaction to infections, autoimmune disorders, or malignancy.

Case report

A 23-year-old healthy Nigerian man was brought to the emergency department with symptoms of relapsing fever, confusion, and lethargy ongoing for 5 days. Past medical history and family history were unremarkable. He had not taken any medications. On physical examination, the patient was stuporous with a Glasgow Coma Scale of 10; he did not have neck stiffness or focal neurological signs. He had splenomegaly and scleral icterus. His vital signs were as follows: blood pressure of 119/70 mmHg, heart rate of 119 bpm, temperature of 39.2 °C, and a respiratory rate of 24 breaths per minute.

Laboratory workup revealed a platelet count of 19,000 cells/mL, hemoglobin of 7.9 g/dL, total white cell count of 5,600 cells/mL, and reticulocyte count of 10.0%. Biochemical tests were as follows: total bilirubin of 15.5 mg/dL, direct bilirubin of 13.5 mg/dL, alkaline phosphatase of 206 IU/L, aspartate transaminase of 123 IU/L, alanine transaminase of 96 IU/L, lactic acid dehydrogenase of 2,023 IU/L, lactate of 4.2 mmol/L, blood urea nitrogen of 28 mg/d:, creatinine of 1.13 mg/dL, and normal electrolytes. Other investigation results were as follows: D-dimer of 6,369 mg/L, haptoglobin of <8 mg/dL, fibrinogen of 508 mg/dL, ferritin of 4,622 mg/L, fasting triglycerides level of 322 mg/dL, and soluble interleukin-2 receptor (i.e., soluble CD25) of 3,677 U/mL (reference range, 223–710 U/mL). Prothrombin time and activated partial thrombin time were in normal range, Direct antiglobulin test was negative, and two sets of blood cultures and urine cultures were all negative. Serology test for hepatitis A, B, and C viruses, cytomegalovirus, Epstein–Barr virus, and human immune deficiency virus were also negative. Abdominal computed tomography scan showed hepatosplenomegaly, and computed tomography scan of the head along with the chest X-ray were normal. Lumbar puncture was not performed due to the patient's low platelet count. Thick and thin blood smears showed ring forms and trophozoites of *Plasmodium vivax*. Polymerase chain reaction of the blood confirmed the patient had *P. vivax* infection.

Given the patient's clinical presentation, the findings on the blood smear, and the fact that he met six out of eight hemophagocytic lymphohistiocytosis diagnostic criteria (Table 1), the diagnosis of cerebral malaria due to *P. vivax*, complicated by HLH was established.

Treatment with intravenous quinidine and doxycycline was initiated. After 24 hours of initiating treatment, the patient's mental status improved drastically and returned to baseline. Quinidine was discontinued because of QTC prolongation and the patient was started on atovaqoune–proguanil. On the 3rd day of hospitalization, the patient's mental status deteriorated again and he developed acute renal failure with a creatinine level of 5.22 mg/dL and a blood urea nitrogen level of 80 mg/dL. Given the glomerular filtration rate of 17 mL/min and the relapse of the patient's mental status, atovaqoune–proguanil was discontinued and the US Center of Disease Control and Prevention was contacted to obtain artesunate that was delivered and initiated on the same day. Over the course of the following 2 days, the patient completed his artesunate course and his mental status returned to normal again. However, his kidney function continued to worsen, which prompted the initiation of hemodialysis. Three daily consecutive blood smears that were done after completing treatment with artesunate

Table 1 Clinicopathological characteristics and data of our patient with malaria-related hemophagocytic lymphohistiocytosis (HLH) diagnosed as per the HLH 2004 criteria.

HLH 2004 diagnostic criteria	Patient's clinical & lab criteria
Fever ⩾38.5 °C	Fever 39.2 °C
Splenomegaly	Present
Peripheral blood cytopenia, with at least 2 of the following: hemoglobin <9 g/dL (for infants <4 wk, hemoglobin <10 g/dL); platelets <100,000/μL; absolute neutrophil count <1000/μL	Platelet count 19,000 cells/mL, hemoglobin of 7.9 g/dL
Hypertriglyceridemia (fasting triglycerides >265 mg/dL) &/or hypofibrinogenemia (fibrinogen <150 mg/dL)	Triglyceride level 322 mg/dL
Hemophagocytosis in bone marrow, spleen, lymph node, or liver	N/A
Low or absent NK cell activity	N/A
Ferritin >500 ng/mL	Ferritin 4,622 mg/L
Elevated soluble CD25 (soluble IL-2 receptor α)	Soluble CD25 level 3,677 U/mL (reference range, 223–710 U/mL)

Note: IL-2 = interleukin-2; N/A = not applicable; wk = weeks.

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were negative for parasitemia. The patient received doxycycline for a total of 14 days. Eventually the patient's kidney function started to improve so hemodialysis was stopped. After a total of 15 days of hospitalization, the patient was discharged in a stable state with normalization of his laboratory results including his blood counts.

Discussion

For many years, *P. vivax* was considered as a more benign infection compared with *P. falciparum*, but recent reports have documented the association of severe syndromes and death with *P. vivax*. In one retrospective study that analyzed the data collected from all the malaria cases reported to the US Center of Disease Control and Prevention between 1985 and 2011, 0.9% of *P. falciparum* cases resulted in death and 9.3% were classified as severe, whereas 0.09% of *P. vivax* cases resulted in death and 1.3% were classified as severe [4]. While pulmonary dysfunction due to respiratory distress, pulmonary embolism, and acute respiratory distress syndrome are the main reasons for mortality in *P. vivax*, other complications like cerebral malaria, bleeding, severe anemia, liver dysfunction, and renal failure are the main reasons for mortality in *P. falciparum* [5].

Both cerebral malaria and HLH are uncommon syndromes that can be associated with *P. vivax* infection and can lead to death if not recognized and treated early. HLH is an inflammatory syndrome that usually presents with fever, cytopenias, hepatitis, and splenomegaly [6]. The pathogenesis of HLH is thought to be due to impaired function of natural killer cells, cytotoxic T cells, and T regulatory cells that leads to an augmented activation of antigen presenting cells (macrophages and histocytes) and CD8+ T cells, which in turn leads to hemophagocytosis in the bone marrow and the reticuloendothelial system. Elevated cytokines also play a role in the syndrome which manifests in high levels of interferon-γ, interleukin-1, and interleukin-6 with the compensatory downregulation of interleukin-10 [7]. According to the HLH 2004 revised diagnostic guidelines published by the Histocyte Society HLH Study Group, the diagnosis of HLH can be made if either a molecular diagnosis consistent with HLH is fulfilled, or if the patient meets at least five of the following eight criteria (Table 1): (1) fever; (2) splenomegaly; (3) cytopenias affecting two or more of three lineages in the peripheral blood; (4) hypertriglyceridemia of more than 265 mg/dL or hypofibrinogenemia of less than 150 mg/dL; (5) hemophagocytosis in bone marrow, spleen, or lymph nodes in the absence of evidence of malignancy; (6) low or absent natural killer-cell activity; (7) ferritin of more than 500 mg/dL; (8) elevated level of soluble CD25 (soluble interleukin-2 receptor) of more than 2,400 U/mL [6].

HLH is classified in to two different conditions: primary and secondary. The primary (familial) HLH usually presents in infancy and early childhood, but can also present *in utero*, adolescence, or adulthood [3,6]. Secondary HLH may develop as a result of an infection, malignancy, or autoimmune disorder [8]. The most common infections associated with HLH are viral infections with Epstein–Barr virus being the most common, and less commonly other herpes viruses (herpes simplex virus, varicella zoster, cytomegalovirus, human herpesvirus 6, and human herpesvirus 8), human immunodeficiency virus, adenovirus, hepatitis viruses, parvo virus, and influenza. HLH has also been associated with bacterial infections including mycobacteria and spirochetes, fungal infections, and parasitic infections due to *Leishmenia donovani*, *P. falciparum*, *P. vivax*, toxoplasma, babesiosis, and strongyloidiasis [8].

Our case is peculiar because it is the first reported case in the US of a patient who not only presented with cerebral malaria due to *P. vivax*, but also had HLH. Most of the case reports of cerebral malaria have been reported in India. These patients, like our patient, were successfully treated with artesunate combination therapy with excellent outcomes [9–11]. Patients with HLH due to infections can usually recover with supportive care and treating the underlying infection. In our case, treating *P. vivax* with artesunate combination therapy resulted in neurologic recovery which obviated the need for dexamethasone, and with continued supportive care the patient clinically recovered.

Most cases of HLH caused by *P. vivax* have been reported in South Korea [12–14] and India [15,16] and also achieved complete recovery by treatment with an antimalarial regimen. Chemotherapy and immunosuppressant therapy with dexamethasone, cyclosporine, and etopside may be indicated in certain situations like familial HLH and severe HLH particularly when associated with Epstein–Barr virus infection [6].

P. vivax infection should always be suspected in patients from endemic areas who present with symptoms of malaria. Severe and persistent cytopenias with neurologic symptoms should raise the possibility of a secondary HLH associated with the infection. Early recognition and treatment are critical to prevent ominous outcomes.

Conflicts of interest

The authors declare no conflict of interest.

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